REMARKS

In response to the Non-Final Office Action mailed July 24, 2008, Applicants have amended claims 1 and 10. Claims 2, 7-9, 12, 13, 18, 19, and 24 have been withdrawn from consideration.

Claim Objections

Claim 4 has been objected to as being allegedly of improper dependent form. Applicant respectfully disagrees and submits that subjects who are susceptible to thrombosis are a subset of subjects who are in need of a treatment to alleviate thrombosis. For example, a subject in need of blood clot dissolution that has thrombosis may remain at risk for development of (other) blood clots. Applicant also submits that the treatment can be both therapeutic (e.g., dissolving an existing blood clot) or prophylactic and that not all subjects in need thereof would use this treatment prophylactically.

According to MPEP 2111.02 Effect of Preamble, the claim preamble must be read in the context of the entire claim. The MPEP quotes *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003): "In considering the effect of the preamble in a claim directed to a method of treating or preventing pernicious anemia in humans by administering a certain vitamin preparation to "a human in need thereof," the court held that the claims' recitation of a patient or a human "in need" gives life and meaning to the preamble's statement of purpose." (MPEP 2111.02) Applicant submits that the preamble points to a subject in need of accelerated blood clot dissolution. Such a subject does not necessarily have an existing blood clot. Therefore, because claim 1 is drawn to a subject in need of accelerated blood clot dissolution, claim 3 is drawn to a subject in need of accelerated blood clot dissolution having thrombosis, and claim 4 is drawn to a subject in need of accelerated blood clot dissolution having thrombosis who remains susceptible to thrombosis (e.g., at risk for re-occurrence), the dependency is proper. Applicant respectfully requests reconsideration of the objection.

Claim Rejections – 35 U.S.C. § 102

Claims 20 and 23 have been rejected as being allegedly anticipated by the publication of Grundy *et al.* The claims have been cancelled, without prejudice or disclaimer, thereby rendering the rejection moot.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 3-6, 10, 11, 14 and 17 have been rejected as being allegedly obvious over Grundy *et al.* in view of Gladstone *et al.*. Further, claims 1, 3-6, 10, 11, 15, and 16 have been rejected as being allegedly obvious over Grundy *et al.* in view of Llevadot *et al.* In the Office Action it is indicated that Grundy *et al.* shows that factor Xaγ is a tPA accelerator. The Examiner alleges that Gladstone *et al.* or Llevadot *et al.* teach that tPA accelerators can be used for the treatment of thrombosis.

Applicant respectfully disagrees and submits to the Examiner's attention the enclosed declaration by Dr. Pryzdial ("Pryzdial Declaration"), a co-inventor of the present patent application and a co-author of the Grundy *et al.* publication. Dr. Pryzdial's qualification as an expert is evidenced by his *Curriculum Vitae* filed herewith as Appendix A.

According to Dr. Pryzdial, "[t]he results presented in Grundy et al. do not show that Factor Xaγ is a tPA accelerator." (Pryzdial Declaration, ¶5) Dr. Pryzdial continues, explaining that

> "In the art, it is known that binding assays (such as those presented in Grundy) are not a reliable predictor of coagulation protein function. In the context of tPA accelerators, the reason is that the accepted gold standard physiological tPA accelerator is the clot itself (i.e. fibrin). The clot is in vast excess over Factor Xaγ. Therefore, according to current art, the clot would logically overwhelm any effects of Factor Xaγ." (Pryzdial Declaration ¶5)

Dr. Pryzdial provides comments from the anonymous peer reviewers who reviewed the grant application that supported this work (Appendix B) and the Grundy manuscript itself before publication (Appendix C), stating:

> "The technology developed by Grundy et al. was reviewed by anonymous peers in a grant application (Appendix B) and prior to its publication (Appendix C). Both of these documents concluded that the *in vitro* results presented in Grundy et al. cannot be used to predict that Factor Xaγ can be used as a tPA accelerator in the context of the clot. In the grant review (Appendix B), it was clearly indicated that:
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> > 'Since the concentration of FV or even that of FX in plasma is at least an order or magnitude less than the concentration of fibrinogen (fibrin), a ratio which would probably be maintained within a clot, it is difficult to envisage a scenario where components of prothrombinase will be cleaved by plasmin in sufficient quantity to compete with fibrin (…) to stimulate tPA-dependent activation of plasminogen.'
>
> "In the manuscript review (Appendix C), it is indicated that,
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> > 'In addition, I wonder whether or not the stimulatory potential of degraded FX(a) on tPA-induced plasminogen activation is relevant in the presence of a great stimulatory potential of intact fibrin…"
> > (Pryzdial Declaration ¶6)

Dr. Pryzdial continues, stating:

> "[c]ontrary to what is currently known in the art, the clot-dissolving experiments presented in the present patent application unambiguously indicate that the clot does not overwhelm effects mediated by Factor Xaγ and consequently, Factor Xaγ may be successfully used to accelerate blood clot dissolution in a subject in need thereof. These experiments provide a reliable prediction that Factor Xaγ will enhance solubilization of the clot *in vivo* in comparison to the experiments

published in Grundy et al., which merely evaluated binding between Factor Xaγ and tPA or plasminogen. (Pryzdial Declaration, ¶7)

Dr. Pryzdial also points out that binding of an agent to another agent does not necessarily predict that the agent will positively affect the activity of either agent. More specifically, Dr. Pryzdial states:

"Further, it is not scientifically sound to predict that any protein that binds tPA or plasminogen *in vitro* will accelerate tPA and clot dissolution. For reasons already cited, the clot is anticipated to overwhelm the effects of other tPA- or plasminogen-binding proteins. Furthermore, the binding protein is believed to require association with both simultaneously to bring the tPA (enzyme) and plasminogen (substrate) into close proximity. This was never shown for Factor Xaγ." (Pryzdial Declaration, ¶8)

"Other than fibrin or fragments of fibrin, I [Dr. Pryzdial] am not aware of published data showing that a protein able to bind either tPA or plasminogen can directly accelerate tPA *in vivo* or in plasma. Many binding-proteins have been identified that have been shown to interact with either tPA or plasminogen, for example: antithrombin III (Dudani, *Thromb Res.*, 2000, 99, 635-41), tetranectin (Heilskov at al, *J. Biol. Chem.*, 1998, 273, 29241-46), fibronectin (Salonen et al., *J Biol Chem.*, 1985, 260, 12302-7.), alpha-enolase (Miles et at., *Biochemistry*, 1991 , 30,1682-91), osteonectin and annexin 2 (Hajjar at al., *J Biol Chem.*, 1996, 271, 21652-9). Of these, to my knowledge, only annexin 2 has been reported to conclusively accelerate tPA to generate plasmin from plasminogen. In complete contradiction to the premise that tPA acceleration and the resulting plasmin formation must result in enhanced clot lysis, annexin 2 was shown to inhibit rather than speed-up fibrin dissolution *in vitro* (Choi et al., *Biochemistry*, 1998, 37, 648-55). Further complicating the picture, when annexin 2 was genetically deleted from mice, clot clearance was apparently prolonged (Ling et al., *J Clin Invest.*, 2004, 113, 38-48)." (Pryzdial Declaration, ¶9)

In view of the art discussed by Dr. Pryzdial showing that even proteins that have been shown to be tPA accelerators are not necessarily effective in clot dissolution, and, indeed, can actually inhibit the process, the binding-only studies of Grundy *et al.* in no way teach or suggest that Factor Xaγ would necessarily be effective in clot dissolution.

Dr. Pryzdial concludes that "it is currently known in the art that *in vitro* binding studies of coagulation factor cannot soundly predict the acceleration of tPA and/or enhancement of fibrinolysis." (Pryzdial Declaration, ¶10)

In light of the above, Applicant respectfully submits that the claims are compliant with 35 U.S.C. § 103 and respectfully requests reconsideration.

The Examiner is authorized to charge any fee deficiencies or credit any overpayments associated with this submission to the Nixon Peabody LLP Deposit Account No. 50-0850. In the event that there are any questions concerning this response, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of the application can be expedited.

Respectfully submitted,

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/Stephen R. Duly/

David S. Resnick (Reg. No. 34,235)
Stephen R. Duly (Reg. No. 56,183)
Nixon Peabody LLP
100 Summer Street
Boston, MA 0 2110
(617) 345-6057 / 1270